Remarks/Arguments

Claims 119-123 are pending in this application. Claim 119 has been amended. No new matter has been added.

I. 35 U.S.C. §§ 101 and 112, First Paragraph –Utility/Enablement

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants strongly disagree and, therefore, respectfully traverse the rejection.

Applicants submit that the data presented in Example 170 starting on page 539 of the specification, and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. Applicants rely upon the gene amplification data of the PRO1097 gene for patentable utility of the claimed PRO1097 polypeptides. This data is clearly disclosed in the instant specification in Example 170, which discloses that the gene encoding PRO1097 showed significant amplification in primary lung and colon tumors. As disclosed in previous response on record, Applicants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1097 gene, that the PRO1097 polypeptide is concomitantly over expressed and has utility in the diagnosis of lung and colon cancers or for individuals at risk for developing lung or colon cancer.

The Examiner asserts that basis of the rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. (Page 3 of the instant Office Action).

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, Applicants have submitted, in their Response filed August 22, 2005, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful

as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung and colon cancers, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Second, Applicants have submitted, in their Response filed September 10, 2004, ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression. Third, Applicants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, the art overwhelmingly shows that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1097 gene, that the PRO1097 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung and colon cancers.

Applicants further submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Applicants' Response filed December 10, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO1097 polypeptides are useful as a diagnostic tools for detecting lung and colon tumors.

Applicant Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed antibodies to PRO1097 polypeptides.

The Examiner has asserted that "[t]he data presented in the specification were not corrected for aneuploidy" and cites references by Fleischhacker et al., Hittelman et al. and Sen et al. in support of the assertion that "[a] slight amplification of a gene does not necessarily

correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." (Pages 4-6 of the instant Office Action).

Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed September 10, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Regarding Sen, Fleischhacker and Hittelman, Applicants agree that while aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer, Sen *et al.* in fact support the Applicants' position that PRO1097 is still useful in diagnosing pre-cancerous lesions or cancer itself. For instance, the art in lung cancer at the time of filing of the instant application clearly described that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged lung lesions which may eventually lead to lung cancer. Many articles published around the effective filing date of this application studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of lung cancer. Based on the well-known art, Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

Applicants further note that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Applicants have shown that the gene encoding PRO1097 was significantly amplified, from 2.114- to 2.532-fold, in five different lung and colon tumors. These values are considered significant based on the Declaration by Dr. Audrey Goddard discussed above. By referring to the 2.114- to 2.532-fold amplification as

"slight," the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary.

The Examiner asserts that the Goddard declaration is not persuasive and alleges that the significance of the amplification can be questioned based on "the strength of opposing evidence." Further, the Examiner asserts that "while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues (Pages 9-10 of the instant Office Action).

Applicants submit that the Goddard Declaration was presented to show what ΔCt values were considered significant in the TaqMan™ assay. The ΔCt values for the DNA that encodes for PRO1097 showed **2.114- to 2.532-fold** amplification in at least five of the tumors and tumor cell lines listed in Table 9, which would be considered significant according to the Goddard Declaration. While this declaration addresses DNA values, it has been presented in this polypeptide case in conjunction with several other supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc. As explained above and in previous Responses, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* were presented to show that in general, gene amplification increases mRNA expression. In addition, Applicants presented Declarations by Dr. Paul Polakis (I and II) to show that, in general, mRNA levels correlate well with protein levels, and the Examiner seems to agree with this point especially in view of the recent Board Decision (Decision on Appeal No. 2006-1469) addressing microarray cases. Presentation of the Goddard Declaration is indeed relevant in this antibody case, because it forms a critical piece of evidence in this case. When placed together with the entire evidence presented for PRO1097, one would logically come to the conclusion that, it is more likely than not, that increased DNA levels generally correlate well with increased mRNA levels (based on, for example, the teachings of supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc.), and further, increased mRNA levels generally correlate well with increased protein levels (the two Polakis Declarations, over 100 references and the recent Board decision). In summary, just as in the microarray cases, Applicants have presented multiple pieces of evidence, such as the Goddard Declaration, the Ashkenazi Declaration, two Polakis Declarations, and several references addressing the relationship between DNA and mRNA/ protein levels, etc., each of which is critical evidence that supports Applicants' position that

PRO1097 polypeptides and the antibodies thereto have utility based on the gene amplification results. Therefore, Applicants believe that a sound case has been presented for utility of PRO1097 as a diagnostic marker, based on the gene amplification data of its corresponding gene in the specification.

Further, the Examiner is required to view the statements in the declaration with the total evidence presented in this case. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.c.P.A. 1976); *In re Piasecki, 745*F.2d. 1015,226 USPQ 881 (Fed. Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."(*In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445,24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton,* "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner (*In re Alton, supra.).* Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Applicants submit that the Patent Office has failed to provide substantial evidence for disregarding the contribution of the Goddard Declaration in establishing the significance of the gene amplification data, which is a critical piece of evidence in this case.

The Examiner addresses the pooled blood controls used in the gene amplification assay and asserts that the controls were not matched, non-tumor lung samples, but rather pooled DNA samples from blood of healthy subjects. (Page 9 of the instant Office Action)

Applicants respectfully submit that the Examiner's position is incorrect because the instant application relies on **genomic DNA** amplification for utility and not cDNA expression. Different types of cells from the same organism should have the same set of genomic DNA. Thus, it does not matter what kind of cells you use for the control as long as the control cells

have the entire genome. Accordingly, a "tissue-matched" control is not necessary in the gene amplification assay.

Applicants further point out that Pennica *et al.* teaches the exact same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance, see page 14718, column 1 and Figure 5 of Pennica *et al.*). Further, the references Bieche *et al.* and Pitti *et al.*, submitted as Exhibits F and G with the Goddard Declaration, also used "pooled normal blood controls" as control. For instance, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay and pooled normal blood controls described in the instant specification, to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2). Thus, contrary to the Examiner's allegations, Pennica *et al,* Pitti *et al.* and Bieche *et al.* in fact, confirm the validity of use of the "pooled blood control" as a negative controls, and indicate that this control was widely utilized in the art at the time of filing of the instant application.

The Examiner has asserted that "[s]ignificant further research is would have been required of the skilled artisan to reasonable confirm that PRO1097 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, thus the asserted utility is not substantial." (Page 8 of the instant Office Action).

As discussed in previous responses of record, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Applicant has identified for the invention that can be viewed as

providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[1] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[2] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO1097 is significantly amplified in certain lung and colon tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1097 gene is amplified, the PRO1097 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO1097 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO1097 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed antibodies to the PRO1097 polypeptide, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Applicants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO1097 polypeptide expression and that the claimed antibodies to the PRO1097 polypeptide have utility in the diagnosis of cancer.

A *prima facie* case of lack of utility has not been established

Applicants respectfully submit that the Examiner has not made a proper *prima facie* showing of lack of utility, because the Examiner has not shown that Applicants' asserted utility is more likely than not incorrect.

The Examiner asserts that "[t]he art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA

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[1] M.P.E.P. §2107.01.

[2] M.P.E.P. §2107 II(B)(1).

levels and polypeptide levels", citing Pennica, Konopka, Sen, Godbout and Li (pages 5-7 of the instant Office Action).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels. As discussed in the previous responses of record, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants have previously cited Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* as collectively teaching that in general, gene amplification increases mRNA expression. Applicants' arguments presented in the previously filed Responses submitted September 10, 2004 and January 10, 2007, Preliminary Amendment submitted July 5, 2006 and Appeal Brief filed January 28, 2008 are hereby incorporated by reference in their entirety.

Pennica *et al.*

The Examiner has cited the abstract of Pennica et al. for its disclosure that "WISP-2 genomic DNA was amplified in colon cancer cell lines and in human colon tumors, but RNA expression was reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (Page 5 of the instant Office Action). From this, the Examiner has concluded that increased copy number does not necessarily result in increased polypeptide expression.

Applicants submit that the standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

Nowhere in the Pennica paper does the author suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. On the contrary, there is a statement in Pennica that says "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*" (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added), which implies that the mRNA/protein correlation does exist, even if not always, but "always" is not required by the utility standard.

The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression . . . .*" (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added). Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Konopka *et al.*

The Examiner has also citeded the abstract of Konopka et al. to establish that "[p]rotein expression is not related to gene amplification but to variation in the level of mRNA produced from a single genomic template." (Pages 5-6 of the instant Office Action).

Regarding Konopka *et al.*, Applicants submit that the Examiner has completely misinterpreted the teachings in the cited reference. Contrary to the Examiner's assertions, Konopka *et al.* does not support the position that DNA amplification is not correlated with mRNA overexpression. Konopka *et al.* show only that, of the cell lines known to have increased abl protein expression, only one had amplification of the abl gene (page 4051, col. 1). This result proves only that increased mRNA and protein expression levels can result from causes other than gene amplification. Konopka *et al.* do not demonstrate that when gene amplification

does occur, it does not result in increased mRNA and protein expression levels, particularly given that the cell line with amplification of the abl gene did show increased abl mRNA and protein expression levels. Furthermore, Konopka *et al.* supports Applicants' position that mRNA levels correlate with protein levels. Konopka *et al.* state that "the 8-kb mRNA that encodes $P210^{c\text{-}abl}$ was detected at a 10-fold higher level in SK-CML7bt-333 (Fig. 3A, +) than in SK-CML16Bt-1 (B, +), which **correlated** with the relative level of $P210^{c\text{-}abl}$ detected in each cell line. Analysis of additional cell lines demonstrated that the level of 8-kb mRNA **directly correlated** with the level of $P210^{c\text{-}abl}$ (Table 1)" (page 4050, col. 2, emphasis added).

Godbout *et al.*

Regarding Godbout, the Examiner has asserted that Godbout et al. teaches that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The Examiner further asserts that Godbout teaches "[i]t is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell." (Page 6 of the instant Office Action).

Applicants have previously made of record three more recent references, published in 2002, by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Applicants' Response filed on Sepetmber 10, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.* Nevertheless, Applicants maintain that Godbout *et al.* report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer. Mechanistic data is not a requirement for the utility requirement. Hence, this rejection is improper. Applicants respectfully submit that, as discussed above, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record), collectively teach that gene amplification increases mRNA expression for large numbers of genes, which have not been identified as being oncogenes or as conferring any selective growth advantage on tumor cells. Thus, the art of

record clearly shows that there is no requirement that a polypeptide must be a known oncogene or a protein otherwise known to be associated with tumor growth, in order for amplification of the gene encoding the protein to correlate with increased protein expression. In fact, as demonstrated by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, examination of gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer.

Li *et al.*

The Examiner also cites Li et al. as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 7 of the instant Office Action).

Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above, the PRO1097 gene showed 2.114 to 2.532 fold amplification in colon and lung tumors, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO1097, would be expected to show a corresponding increase in transcript expression.

The Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1097 has utility. As discussed above, the law does not require that DNA amplification

is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

In response to Applicants' argument that the discordance may reflect methodologic differences, the Examiner asserts that "Li et al. did not limit their studies to genes that were amplified at less than 2-fold." In support of this assertion, the Examiner cites the first paragraph of the Supplemental Material. (Page 12 of the instant Office Action).

Applicants respectfully point out that the Examiner has misinterpreted the methodology disclosed in the supplemental material. The evidence cited by the Examiner pertains to the inclusion criteria of the probes used for defining amplicons. In the second paragraph entitled "Relationship between genomic copy number and gene transcript level", the authors state that "[f]or each gene, the CGH data were represented by a vector that was labeled '1' for genomic overrepresentation (including amplification) ratio greater than 1.40 and '0' for no genomic overrepresentation." Nevertheless, the Examiner acknowledges that the alleged 2-fold amplification criteria would only apply to some of the samples. The Examiner has not established that a correlation does not exist in samples based solely on this threshold.

Hanna and Mornin

The Examiner asserts that "Hanna evidences that the level of protein expression must be tested empirically to determine whether or not the protein can be used as a diagnostic marker for a cancer." The Examiner further asserts that Hanna teaches that HER-2/neu testing will utilize FISH and IHC to better establish a correlation. From this the Examiner concludes that Hanna and Mornin supports the instant rejection. (Page 16 of the Final Office Action).

Applicants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Applicants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression. Further, the

authors make clear that the screening strategy is "based upon the above considerations," that is, the selection of patients who should receive treatment with Herceptin, as discussed in the immediately preceding paragraph. Thus the purpose of measuring both protein and gene levels is not merely further experimentation, but further characterization of the tumors into medically relevant categories.

Applicants have clearly shown that the gene encoding the PRO1097 polypeptide is amplified in at least five primary lung and colon tumors. Therefore, the PRO1097 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1097 gene, that the PRO1097 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration and the Hanna article. The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna article as experiments involving further characterization of the PRO1097 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO1097 polypeptide, but the tumors in which the gene encoding PRO1097 is amplified. The claimed antibodies to the PRO1097 polypeptide are therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

In summary, the Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1097 has utility. As discussed above, the law does not require that DNA amplification is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper,

heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have incrased mRNA and protein levels

As discussed above and in detail previously, Applicants have provided ample evidence in the form of articles from the art, like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and over a 100 references and Declarations by experts in the field of oncology and gene expression, i.e.: the Declarations by Dr. Audrey Goddard, Dr. Paul Polakis (I and II) and Dr. Avi Ashkenazi, to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

The Examiner asserts that "[i]n order for PRO1097 polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1097 mRNA or PRO1097 polypeptide levels in lung or colon tumors have been brought forth on the record." (Page 5 of the instant Office Action).

The Examiner's reference to the lack of necessary correlation or accurate prediction in some of the rejections clearly shows that the Examiner again applies an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. As discussed below, the references cited by the Examiner do not suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels.

In contrast, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of

record in Applicants' Response filed September 10, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, as the Examiner has acknowledged, the art teaches that, in general, there is a correlation between mRNA levels and polypeptide levels.

Accordingly, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1097 gene, that the PRO1097 polypeptide is concomitantly overexpressed. Thus, the claimed antibodies to the PRO1097 polypeptide have utility in the diagnosis of cancer.

Applicants therefore respectfully request withdrawal of the rejections of Claims 119-123 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **50-4634** Attorney Docket No.: **123851-181895 (GNE-2730P1C30)**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 30, 2008

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